

CHOLESTEROL
LOWERING IN
THE PATIENT
WITH CORONARY
HEART DISEASE

PHYSICIAN
MONOGRAPH



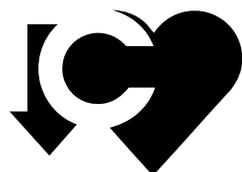
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PHYSICIAN MONOGRAPH

NATIONAL INSTITUTES OF HEALTH

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CONTENTS

Cholesterol and the CHD Patient	1
Review of the Evidence	1
Recent Clinical Trials	1
Scandinavian Simvastatin Survival Study	1
Cholesterol and Recurrent Events Trial	2
Post Coronary Artery Bypass Graft Trial	2
Meta-Analysis of Previous Trials	3
Review of Angiographic Trials	3
Unstable Plaque	4
Magnitude of the Benefit From Cholesterol Lowering in CHD Patients	4
Conclusion	5
Overview of the ATP II Guidelines	5
Management of Cholesterol Levels In CHD Patients	7
Measurement	7
Dietary Therapy	8
Step II Diet	8
How To Make the Step II Diet Work	9
Physical Activity	10
Weight Control	11
Diet Initiation, Monitoring, and Followup	12
Drug Treatment	12
When To Initiate Drug Treatment	12
Drug Selection	13
Monitoring and Followup	17

Adherence	18
Role of the Physician	18
Role of the Nurse	19
Role of the Registered Dietitian	19
Role of the Pharmacist	19
Strategies To Enhance Adherence	19
Summing Up	21
Patient Handouts	22
Patient Instructions for Taking Statins	22
Patient Instructions for Taking Resin Therapy	23
Patient Instructions for Taking Nicotinic Acid (Niacin)	25
References	27
Additional Materials	28
Order Form	31

CHOLESTEROL LOWERING IN THE PATIENT WITH CORONARY HEART DISEASE

CHOLESTEROL AND THE CHD PATIENT

Recent clinical trials have proven conclusively that lowering low density lipoprotein (LDL) cholesterol levels in patients with established coronary heart disease (CHD) sharply reduces the risk of myocardial infarction (MI), death from CHD, and death from all causes. The benefit of cholesterol-lowering therapy extends even to patients with average cholesterol levels. The goal for cholesterol lowering in CHD patients is an LDL-cholesterol of 100 mg/dL or less.

In light of the evidence, cholesterol lowering should be a routine feature of the clinical management of CHD. Unfortunately, many CHD patients are receiving inadequate or no therapy to lower cholesterol.

This monograph was developed to help physicians improve the health and prolong the lives of patients with CHD. It aims to do four things: (1) review the evidence that cholesterol lowering is highly beneficial in CHD patients, (2) summarize the basic Adult Treatment Panel II (ATP II)¹ guidelines as they pertain to CHD patients, (3) provide guidance on initiating diet and drug treatment, and (4) offer practical advice on ways to improve adherence.

REVIEW OF THE EVIDENCE

The presence of established CHD confers a high risk for the occurrence of subsequent coronary events and CHD mortality. Men and women with CHD have about five to seven times the risk of developing a myocardial infarction as those with no previous clinical manifestations of coronary disease. Recent observational studies

have shown that LDL-cholesterol levels are significant predictors of future MI in patients with established CHD. This relationship holds even for CHD patients with cholesterol levels in the relatively low range.

Over the past three decades, the medical community has been accumulating evidence regarding cholesterol lowering in patients with CHD. Three recent clinical trials—4S,² CARE,³ and Post CABG⁴—that achieved large reductions in cholesterol levels through the use of statin drugs have provided unequivocal evidence that lowering cholesterol produces large benefits in CHD patients. These trials, in conjunction with meta-analyses of previous clinical trials and angiographic studies, support the National Cholesterol Education Program (NCEP) recommendation that aggressive cholesterol lowering should be a standard element in the care of patients with CHD.

Evidence of the Benefits of LDL-Cholesterol Lowering in CHD Patients

- Recent randomized clinical trials (4S, CARE, and Post CABG)
- Meta-analysis of previous clinical trials
- Angiographic trials

Recent Clinical Trials

Scandinavian Simvastatin Survival Study

The Scandinavian Simvastatin Survival Study (4S)² was a randomized placebo-controlled clinical trial involving 4,444 patients who had a history of angina pectoris or MI and serum

cholesterol levels between 213 and 310 mg/dL. The patients (81 percent male, 19 percent female, ages 35 to 70 years at enrollment) were placed on a cholesterol-lowering diet and were randomized to double-blind treatment with either the statin drug simvastatin or a placebo. The primary endpoint was total mortality.

Over the median 5.4 years of followup, simvastatin therapy resulted in a mean lowering of 25 percent in total cholesterol and 35 percent in LDL-cholesterol. The treatment group experienced a 34 percent reduction in major coronary events, a 42 percent reduction in CHD mortality, a 37 percent reduction in revascularization procedures (coronary artery bypass surgery or angioplasty), and a 30 percent reduction in total mortality. Older patients (≥ 65 years old) and women also showed a reduction in CHD morbidity and mortality with cholesterol lowering. In this study, a very large degree of cholesterol lowering produced no increase in noncardiovascular mortality—in particular, no increase in deaths from cancers or from suicide, homicide, or accidents.

Key Findings From 4S

Cholesterol levels

25% ↓ in total cholesterol

35% ↓ in LDL-cholesterol

Endpoints

34% ↓ in major coronary events

42% ↓ in CHD mortality

37% ↓ in revascularization procedures

30% ↓ in total mortality

Cholesterol and Recurrent Events Trial

The Cholesterol and Recurrent Events (CARE) trial,³ a 5-year double-blind study, documented for the first time a benefit of cholesterol lowering in CHD patients with average cholesterol levels. The CARE study enrolled 4,159 patients (86 percent male, 14 percent female) ages 24 to 75 who had suffered an MI in the 2 years before study enrollment. Total cholesterol levels of partici-

pants averaged 209 mg/dL at study initiation. Pravastatin was used to lower cholesterol levels in the treatment group, and the primary endpoint was death from CHD or symptomatic nonfatal MI.

Pravastatin therapy resulted in a mean reduction of 20 percent in total cholesterol and 28 percent in LDL-cholesterol. The treatment group had a 24 percent reduction in fatal CHD and nonfatal MI and a 27 percent reduction in revascularization procedures. Women and older patients (≥ 60 years of age) showed even greater reductions in major coronary events. As in 4S, the large reductions in cholesterol levels produced no significant increase in noncardiovascular mortality, including deaths from cancers or from suicide, homicide, or accidents. Although there were more breast cancer cases in the pravastatin group, no previous or ongoing trials with pravastatin or other statins have shown this connection. This study demonstrates the benefits of cholesterol lowering in CHD patients whose cholesterol is average.

Key Findings From CARE

Cholesterol levels

20% ↓ in total cholesterol

28% ↓ in LDL-cholesterol

Endpoints

24% ↓ in CHD mortality and nonfatal MI

27% ↓ in revascularization procedures

Post Coronary Artery Bypass Graft Trial

The Post Coronary Artery Bypass Graft (Post CABG) trial⁴ was a multicenter, double-blind, randomized, controlled trial of 1,351 patients (92 percent male, 8 percent female) ages 21 to 74 years with existing saphenous vein coronary bypass grafts (SVG) placed 1 to 11 years previously, with LDL-cholesterol levels between 130 and 175 mg/dL. This study compared the efficacy of aggressive versus moderate LDL-cholesterol-lowering therapy in delaying the progression of SVG atherosclerosis as measured by angiography after 4 to 5 years on therapy.

Through the use of a combined regimen of lovastatin and cholestyramine resin, the aggressive cholesterol-lowering group achieved a mean LDL-cholesterol of 93 to 97 mg/dL, and the moderate cholesterol-lowering group achieved a mean LDL-cholesterol of 132 to 136 mg/dL.

In the Post CABG trial, aggressive LDL-cholesterol lowering (to a mean level of 93 to 97 mg/dL) produced a 31 percent reduction in the progression of atherosclerosis in the grafts, as compared to moderate LDL-cholesterol lowering, and reduced the need for repeat revascularization. The results of this study support the NCEP recommendation to lower LDL-cholesterol in CHD patients to 100 mg/dL or less.

Key Findings From Post CABG

Cholesterol levels

LDL-cholesterol 93–97 mg/dL with aggressive lowering (vs. 132–136 mg/dL with moderate lowering)

Endpoints

31% ↓ in plaque progression

29% ↓ in revascularization procedures
($p=0.03$: not statistically significant when corrected for multiple testing)

Meta-Analysis of Previous Trials

The 4S, CARE, and Post CABG trials provide conclusive proof of the benefits of cholesterol lowering in CHD patients, but they are not the first studies to demonstrate these effects. Their results are consistent with earlier trials that typically achieved lesser degrees of cholesterol lowering (approximately 10 percent in most cases). A 1993 meta-analysis* by Rossouw, which appears in the ATP II report¹ and is based on earlier analyses^{5,6} of secondary prevention trials, showed that cholesterol lowering to a more modest extent

than in 4S, CARE, and Post CABG reduced nonfatal MI by approximately 26 percent, fatal MI by about 14 percent, and total mortality by about 9 percent.

Meta-Analysis of Previous Trials

Cholesterol levels

Modest cholesterol lowering (approximately 10%)

Endpoints

26% ↓ in nonfatal MI

14% ↓ in fatal MI

9% ↓ in total mortality

Review of Angiographic Trials

Angiographic studies¹⁴ have shown that, in patients with coronary atherosclerosis, intensive cholesterol lowering—often to LDL-cholesterol levels of 100 mg/dL or below—retards the rate of progression and in some patients leads to regression of atherosclerotic lesions. Favorable results have been observed whether cholesterol lowering was achieved by lifestyle modification (dietary therapy and physical activity), drug therapy, or partial ileal bypass surgery. In these studies, relatively small improvements in lumen diameter were observed; these are unlikely to account for the quite large reductions that occurred in the incidence of clinical CHD events. The fact that these significant reductions have been observed in the treated groups after only 2 years of treatment most likely indicates that the instability of plaques (which leads to fissuring, thrombosis, and intramural hemorrhage) is reduced as well. A reduction in CHD events resulting from cholesterol intervention has been observed even in patients who were not selected because of high cholesterol levels but had pretreatment levels in the so-called “normal” range.

* Studies included in the 1993 meta-analysis: Medical Research Council's low-fat diet trial,⁷ Medical Research Council's soyabean oil trial,⁸ Scottish Society of Physicians' clofibrate trial,⁹ Stockholm Ischaemic Heart Disease Secondary Prevention Study,¹⁰ Coronary Drug Project's clofibrate trial,^{11,12} Coronary Drug Project's niacin trial,^{11,12} and Program on the Surgical Control of the Hyperlipidemias.¹³

Angiographic Trials

Cholesterol levels

- Intensive LDL ↓ – often to 100 mg/dL or below

Results

- Slowed progression of plaque
- Regression of plaque in some patients
- Reduced CHD events

Unstable Plaque

To understand how modest regression in a small number of lesions can be associated with a large and relatively rapid reduction in the frequency of clinical events, it is necessary to review the characteristics of the unstable lesion that typically precipitates a clinical event.

Most patients who die from an MI have a thrombosed arterial segment associated with a fissured fibrous cap of an atherosclerotic plaque. This type of lesion constitutes only 10 to 20 percent of all atherosclerotic lesions but accounts for 80 to 90 percent of acute clinical events. Fissuring is associated with a large accumulation of core lipid in the plaque and with a high density of lipid-laden macrophages in its thinned fibrous cap. In the clinical setting, intensive cholesterol lowering greatly reduces the likelihood that plaques will undergo rupture and lead to clinical events such as sudden death, MI, or worsening angina requiring coronary artery bypass graft or angioplasty.

The reduction of clinical events seen in these angiographic trials can be best explained by the

Through cholesterol lowering, unstable lesions are stabilized, their tendency to rupture is reduced, and the clinical event rate is decreased accordingly.

cholesterol-lowering therapy selectively depletes or regresses that relatively small but dangerous

relationship between the lipid and foam cell content of the plaque and its likelihood of fissuring and by the effects of cholesterol lowering on plaque morphology. Trial results support the hypothesis that

subgroup of fatty lesions containing a large lipid core and dense clusters of intimal macrophages. As a result, these lesions are stabilized, their tendency to rupture is reduced, and the clinical event rate is decreased accordingly.

Magnitude of the Benefit From Cholesterol Lowering in CHD Patients

CHD patients have been shown in clinical trials to experience large benefits from cholesterol lowering. In 4S, CHD mortality was reduced by 42 percent and total mortality by 30 percent.

Major coronary events were reduced by 34 percent in 4S and by

24 percent in CARE. Estimates from the CARE study suggest that aggressive cholesterol-lowering treatment of 1,000 CHD

patients over 5 years can be expected to avert 153 cardiovascular events if the patients are similar to those in CARE, 207 if they are all over 60, and 228 if they are all women. Estimates derived from the work of the 4S authors suggest that treatment of 1,000 CHD patients over 6 years can be expected to preserve the lives of 40 of the 90 patients who would otherwise die from CHD, prevent 70 of the expected 210 non-fatal MIs, and avoid revascularization procedures in 60 of 190 patients. Among the approximately 3.5 million Americans with CHD and elevated cholesterol levels similar to those of 4S patients, cholesterol lower-

ing should prevent about 140,000 deaths, 270,000 MIs, and 585,900 hospitalizations for CHD. An even greater impact on

the lives and health of the 12 to 13 million people with CHD can be expected from extending the eligibility criteria for aggressive therapy to those used in the CARE study.

Treating only the 3.5 million 4S-like patients prevents 140,000 deaths, 270,000 MIs, and 585,900 hospitalizations

Extending the criteria for aggressive therapy to those used in CARE will produce an even greater impact.

Clearly, cholesterol lowering offers CHD patients impressive benefits. The trial data suggest that these effects are as large as, if not larger than, those from aspirin or beta-blockers. It should be recognized, however, that as worthwhile as it is to lower cholesterol in established CHD, once the extent of atherosclerosis in the coronary arteries is as great as it is in CHD patients, plaque stabilization through cholesterol lowering can go only so far. Thus, in 4S, the 42 percent reduction in CHD mortality means that 58 percent was left untouched. Given the very high baseline rate of CHD death in patients with established CHD, the 58 percent that remains after cholesterol-lowering therapy is still an unacceptably high rate of CHD death. With newer agents that promise to lower LDL-cholesterol by 50 to 60 percent, the reduction in CHD risk will probably be larger, but even so, the residual morbidity and mortality from CHD is still likely to be greater than in the population without CHD. This implication of the clinical trial data reinforces the need for a strong complementary program of primary prevention to help reduce the burden of atherosclerosis in our society and prevent the development of CHD in the first place.

Conclusion

Clinical trial evidence from the 4S, CARE, and Post CABG trials, as well as from meta-analysis of earlier trials and angiographic studies, shows that aggressive cholesterol lowering in CHD patients will reduce the risk for a future MI and CHD death, thereby improving the health and prolonging the lives of many CHD patients. The overall body of evidence supports the NCEP recommendation to lower LDL-cholesterol in CHD patients to 100 mg/dL or less.

OVERVIEW OF THE ATP II GUIDELINES

The NCEP ATP II guidelines call for aggressive cholesterol lowering in patients with CHD or other clinical atherosclerotic disease—namely, MI, angina, CABG or angioplasty, peripheral arterial disease, abdominal aortic aneurysm, or symptomatic carotid artery disease (see Table 1). These patients all have a very high risk for CHD events and thus require intensive treatment to lower cholesterol levels. The goal of cholesterol-lowering therapy in patients with CHD or other atherosclerotic disease is an LDL-cholesterol level ≤ 100 mg/dL.

In CHD patients, the LDL goal is ≤ 100 mg/dL.

Table 1. Atherosclerotic Disease: Candidates for Aggressive LDL-Cholesterol Lowering

Coronary Heart Disease

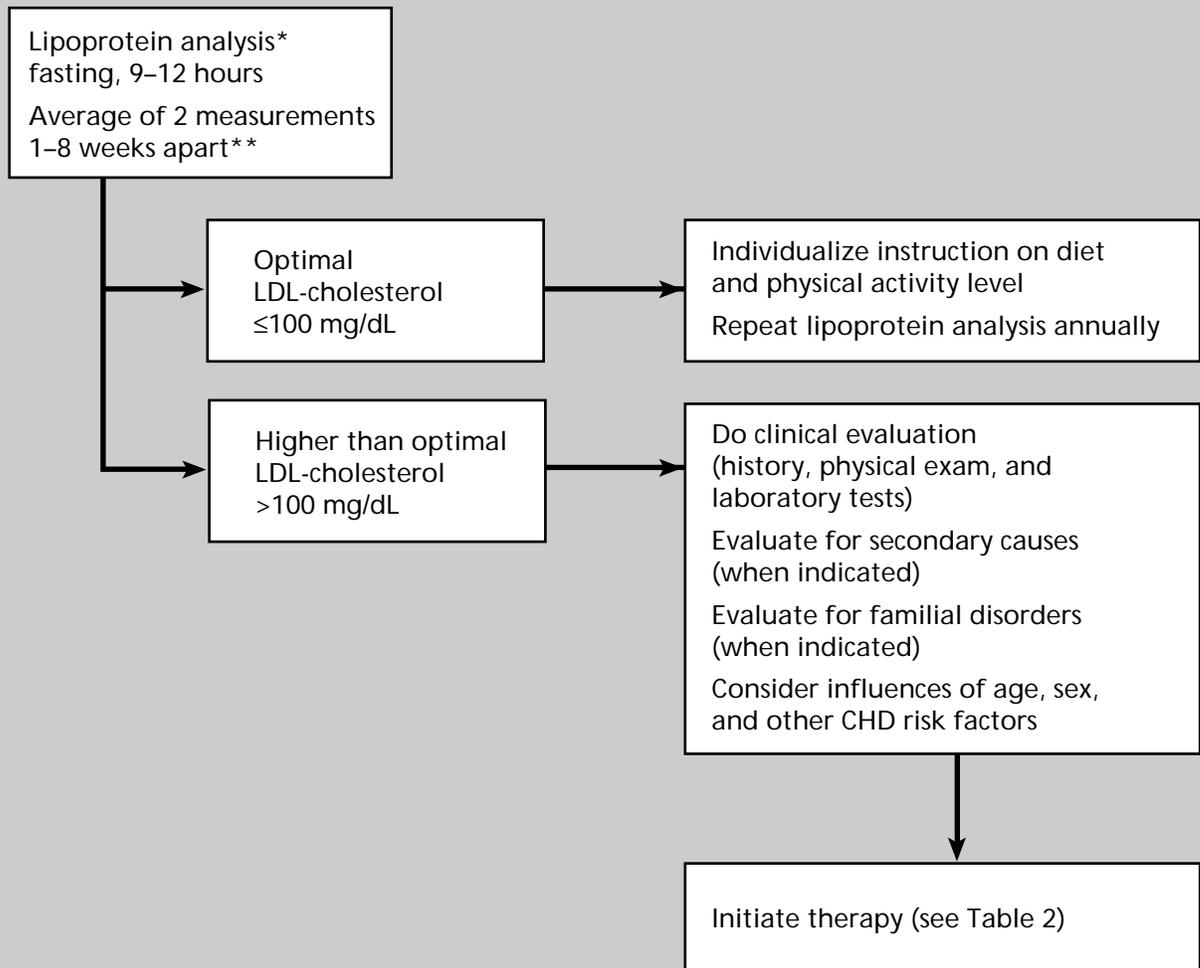
- Myocardial infarction
- Angina pectoris
 - Unstable angina
 - Stable angina
- Coronary artery procedures
 - Coronary artery bypass surgery
 - Angioplasty

Other Forms of Atherosclerotic Disease

- Peripheral arterial disease
- Abdominal aortic aneurysm
- Symptomatic carotid artery disease

All men and women who have established CHD should have a fasting lipoprotein analysis for LDL-cholesterol determination on at least two occasions, 1 to 8 weeks apart (see Figure 1). If the two LDL-cholesterol values differ by more than 30 mg/dL, a third test should be performed;

Figure 1. Secondary Prevention in Adults With Evidence of CHD: Classification Based on LDL-Cholesterol



* Lipoprotein analysis should be performed when the patient is not in the recovery phase from an acute coronary or other medical event that would lower their usual LDL-cholesterol level.

** If the first two LDL-cholesterol tests differ by more than 30 mg/dL, a third test should be obtained within 1-8 weeks and the average value of the three tests used.

the average of all three would then be used. Blood samples should be collected from patients who have fasted for at least 9 to 12 hours (i.e., nothing by mouth of caloric value).

Table 2 summarizes the cutpoints for initiating dietary therapy and, when appropriate, adding drug treatment. If the LDL-cholesterol is higher than 100 mg/dL, maximal dietary therapy with

the Step II diet (see page 8), together with physical activity and weight control, should be initiated. For many patients, this will be sufficient. For many others, however, it will be necessary to add drug treatment, since the goal LDL-cholesterol of 100 mg/dL is quite low. If and when it becomes apparent that the target LDL-cholesterol cannot be reached by diet and life habit changes alone, drug therapy should be considered.

Table 2. LDL-Cholesterol-Lowering Therapy in CHD Patients

	Initiate Dietary Therapy	Add Drug Treatment	Goal
LDL-cholesterol level	>100 mg/dL	≥130 mg/dL	≤100 mg/dL

In general, if the patient's stable baseline LDL-cholesterol is ≥ 130 mg/dL, it is not likely to be lowered to ≤ 100 mg/dL with dietary therapy alone, and a combination of diet and drug treatment is warranted. If the baseline LDL-cholesterol is 100 to 129 mg/dL, diet therapy should be tried for 6 weeks. Whether to initiate drug therapy for patients whose LDL-cholesterol remains between 100 and 129 mg/dL after intensive dietary therapy depends on a variety of factors and must be left to the judgment of the physician. Many authorities believe it is prudent to initiate drug therapy to maximize reduction of LDL-cholesterol levels, but the physician will have to consider the potential side effects and costs of drug therapy in arriving at a decision. Likewise, if the LDL-cholesterol level is between 100 and 129 mg/dL after single-drug therapy, a decision to raise the dose or add a second drug will have to be based on clinical judgment.

All CHD patients should be encouraged to maintain life habit changes (diet, physical activity, and weight control) even when on drug therapy. These changes will not only help maximize the reduction in LDL-cholesterol and minimize the dose of medication but will also reduce CHD risk by other mechanisms, such as raising high density lipoprotein (HDL) and lowering very low density lipoprotein (VLDL) levels, lowering blood pressure and improving glucose tolerance, and lessening the danger of acute coronary thrombogenesis.

MANAGEMENT OF CHOLESTEROL LEVELS IN CHD PATIENTS

Measurement

The recommended lipoprotein analysis (see page 5) should be performed when the patient is metabolically stable. If the patient has had an acute myocardial infarction, cholesterol levels may be lower than usual for up to 12 weeks thereafter, but a preliminary measurement of cholesterol during the acute phase provides an approximation that can assist with initial management decisions. Any acute insult, such as an acute MI, can set into motion a series of metabolic responses. Mobilization of free fatty acids leads to elevated triglyceride levels and the depression of LDL- and HDL-cholesterol levels. If possible, a lipoprotein profile should be obtained immediately on admission (within a few hours of the MI), before these metabolic effects have accumulated and while levels may still reflect a patient's pre-event cholesterol status. In addition, a lipoprotein profile should be obtained at a time close to discharge. If the LDL-cholesterol at discharge is ≥ 130 mg/dL, relatively firm decisions about cholesterol-lowering treatment can be made then, since the LDL level will likely be higher later when the patient has not only recovered from the acute event but reestablished normal habits.

CHD patients who have not had a recent acute MI but who are acutely ill, or those with recent trauma, surgery, acute infection, a change in usual diet, weight loss, or pregnancy, should be rescheduled for lipid testing because the lipid levels in such patients may not be representative of their usual levels.

The choice of a laboratory is an important issue because there is variability in the accuracy and reliability with which laboratories measure cholesterol. The physician should seek a laboratory that participates in a reliable standardization program, preferably one that has its lipid assays standardized through one of the National Network Laboratories of the Centers for Disease Control and Prevention.

To minimize the effects of posture, which can alter the cholesterol value by changing plasma volume, venipuncture should be carried out in patients who have been sitting for at least 5 minutes, and the tourniquet should be used for as brief a period as possible. It is preferable to collect the blood in tubes without anticoagulant (for serum) since NCEP ATP II cutpoints are serum values, but it is acceptable to use tubes containing EDTA (ethylenediaminetetraacetic acid, for plasma). To convert plasma values to serum, multiply the plasma values by 1.03.

If the fasting triglyceride value is below 400 mg/dL, this value can be divided by 5 to estimate the VLDL-cholesterol level. Because the total cholesterol level is the sum of LDL-cholesterol, HDL-cholesterol, and VLDL-cholesterol, LDL-cholesterol can be calculated as follows:

$\text{LDL-Cholesterol} = \text{Total Cholesterol} - \text{HDL-Cholesterol} - \frac{\text{Triglycerides}}{5}$
<p>All quantities are in mg/dL.</p>

For patients with triglyceride values of more than 400 mg/dL, estimation of LDL-cholesterol in this way is not accurate, and ultracentrifugation in a specialized laboratory is required for accuracy.

All patients with CHD and an LDL-cholesterol >100 mg/dL should be evaluated thoroughly to guide cholesterol management. The clinical evaluation—history, physical examination, and laboratory tests—has several aims. The first is to determine whether the elevated LDL-cholesterol is secondary to another condition, such as:

- Diabetes mellitus
- Hypothyroidism
- Nephrotic syndrome
- Obstructive liver disease
- Drugs (e.g., progestins, anabolic steroids, corticosteroids, and certain antihypertensive agents)

A second aim is to determine whether a genetic disorder is present. A family history and cholesterol measurement in the patient's first-degree relatives may uncover additional patients with a genetic dyslipidemia who need therapy before they develop clinical CHD. A third aim is to be able to use information about the patient's overall CHD risk status, including age, sex, and other CHD risk factors, in establishing a treatment program directed at the lipid problems.

Dietary Therapy

Dietary therapy is an essential element in the treatment of all CHD patients whose LDL-cholesterol level is >100 mg/dL. Dietary therapy addresses the major contributors to an elevated LDL-cholesterol level: excess intakes of saturated fat and cholesterol, and an imbalance between energy expenditure and caloric intake leading to obesity. Accordingly, a program of dietary therapy and life habit modification reduces the intakes of saturated fat and cholesterol, increases physical activity, and seeks to restore caloric balance to control weight. The goal is not a temporary "diet," but a permanent change in eating patterns, accompanied by increased physical activity appropriate for the patient's cardiac status.

Step II Diet

The cornerstone of dietary therapy for the CHD patient is the Step II diet (see box, page 9). Reduction of saturated fat intake is crucial, since saturated fat raises LDL-cholesterol more than any other dietary component. Reduction of total fat facilitates a decrease in saturated fat and caloric intake but does not lower LDL-cholesterol per se. Dietary cholesterol raises the serum

cholesterol level in many people, and epidemiologic studies suggest that it increases risk for CHD beyond its serum cholesterol-raising effect. Caloric balance is important for achieving desirable weight; correcting obesity, even in mildly overweight patients, helps lower LDL-cholesterol, reduce VLDL-cholesterol and triglycerides, and raise HDL-cholesterol levels.

Step II Diet	
Saturated fat	<7 percent of total calories
Total fat	≤30 percent of total calories
Cholesterol	<200 mg/day
Total calories	To achieve and maintain desirable weight

Dietary equations predict that the Step II diet will reduce LDL-cholesterol levels by about 10 to 20 percent in CHD patients who are consuming an average American diet. Many CHD patients, however, have higher intakes of saturated fat and cholesterol and higher serum cholesterol levels than average and will thus achieve an even greater reduction in LDL levels.

How To Make the Step II Diet Work

The Step II diet should meet the Recommended Dietary Allowances while providing a variety of foods from all food types. Generally, dairy and meat products should be of the low-fat or nonfat variety, and meats should be lean. It is generally not necessary or desirable to eliminate dairy products or meats (or any major food group, for that matter) from a cholesterol-lowering eating pattern. A variety of nutritious and palatable foods can be consumed as part of a fat-modified diet aimed at lowering serum cholesterol levels and reducing CHD risk. This overall eating pattern also may help prevent other diet-related chronic diseases.

To decrease the intake of saturated fat, total fat, and cholesterol, the emphasis of the Step II diet should be on consumption of:

- fruits and vegetables
- breads, cereals, rice, legumes, and pasta
- skim or 1 percent milk and nonfat or low-fat milk products
- lean meat, poultry, and fish

The following tips will help your patients choose foods for the Step II diet. Deliver at least a few of the most salient points yourself; the remainder can be conveyed by a registered dietitian, other qualified nutritionist, or member of your office staff. Assistance from a dietitian can be particularly helpful in facilitating maintenance of the Step II diet in CHD patients.

To cut back on saturated fats, advise patients to choose:

- Poultry, fish, and lean cuts of meat. Remove the skin from chicken and trim the fat from meat before cooking.
- Skim or 1 percent milk instead of 2 percent or whole milk.
- Cheeses with no more than 3 grams of fat per ounce. Cut down on full-fat processed, natural, and hard cheeses (like American, brie, and cheddar).
- Low-fat or nonfat yogurt, sour cream, and cream cheese instead of the high-fat varieties.
- Liquid vegetable oils that are high in unsaturated fat (these include canola, corn, olive, and safflower oil).
- Margarine made with unsaturated liquid vegetable oil as the first ingredient rather than hydrogenated or partially hydrogenated oil. Choose tub or liquid margarine or vegetable oil spreads. The softer the margarine, the more unsaturated it is. If sodium intake needs to be controlled, try unsalted margarine. Use the food label to choose margarines with the least amount of saturated fat.

- Fewer commercially prepared and processed foods (e.g., cakes, cookies, and crackers) made with saturated or hydrogenated fats or oils.
- Foods high in starch and fiber such as whole wheat breads and cereals instead of foods high in saturated fats.

Reducing saturated fat intake will also help control dietary cholesterol since foods high in saturated fat are often, but not always, high in cholesterol. Two additional points for patients to remember when cutting back on dietary cholesterol are:

- Strictly limit organ meat (such as liver, brain, and kidney).
- Eat a total of two or fewer egg yolks a week (as whole eggs or in prepared foods). Try substituting two egg whites for each whole egg in recipes, or using an egg substitute.

Foods high in starch and fiber are excellent substitutes for high saturated fat foods. To help patients include more foods high in starch and fiber, advise them to choose:

- More vegetables and fruits. It is recommended that Americans eat 5 servings of fruits and vegetables every day. They are low in saturated fat and total fat and have no cholesterol. Fruits and vegetables are good sources of starch, fiber, vitamins, and minerals and are low in sodium. They are also low in calories (which helps with weight control) except for avocados and olives, which are high in both fat and calories. Many fruits and vegetables are also high in antioxidants such as vitamin C, vitamin E, and beta-carotene. A diet high in these fruits and vegetables may also help lower risk for heart disease.
- Whole grain breads and cereals, pasta, rice, and dry peas and beans.

Patients should also be advised to use low-fat methods of cooking:

- Bake, broil, microwave, poach, or roast instead of breading and frying.
- When roasting, place the meat on a rack so the fat can drip away.

Physical Activity

Physical activity is important for all CHD patients, whether they are overweight or not. To be effective, an exercise program should be individualized with respect to the patient's physical fitness, cardiac status, and desired forms of activity. Ongoing group exercise programs such as cardiac rehabilitation, when available, are very conducive to adherence to increased physical activity, as is the support of an exercise companion.

Many CHD patients, especially those recovering from an acute event, will need additional instruction and monitoring when initiating a physical activity program. Cardiac rehabilitation programs can meet this need by providing monitored exercise facilities, trainers, and instruction on life habit changes.

A physical activity program should be prescribed for the CHD patient by the physician, taking into account the patient's cardiac status. When aerobic activity is appropriate, activities such as brisk walking, jogging, swimming, bicycling, and tennis that place moderate stress on the cardiorespiratory system can be included. The prescription should include the amount, intensity, and frequency of desired activities. In CHD patients, the intensity and duration of activity should be increased gradually by the physician over a few weeks or, in the case of obese or very sedentary patients, over several months and regulated by their physician. Available data indicate that higher levels of activity will lead to greater rates of weight loss and greater degrees of LDL reduction and HDL increase.

Once an overweight patient has achieved the desired body weight, it is most important that a regular exercise program be maintained permanently as caloric intake is liberalized. Thus, an average adult man weighing 150 pounds may be able to resume a 2,500-calorie diet after weight loss provided that a higher level of energy expenditure is maintained. Experience has shown that weight loss is unlikely to be maintained in persons who resume their original low level of energy expenditure.

Although brisk walking for 20 to 30 minutes three times a week can improve cardiorespiratory fitness, this level of activity may be insufficient to prevent weight regain. Increased physical activity nevertheless is desirable in nonobese patients because persons who maintain a moderately high level of physical activity are less likely to gain weight as they age and are therefore likely to maintain lower levels of atherogenic lipoproteins, including LDL, and a higher HDL level.

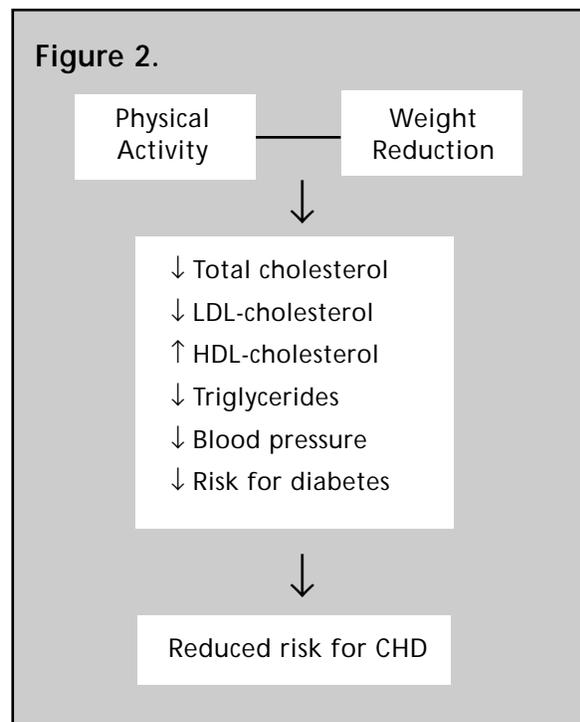
Successful long-term reduction in CHD risk will depend on the patient's ability to integrate physical activity into his or her life. Continued support and encouragement of new behaviors, as well as acknowledgment of beneficial risk reductions, are part of the physician's role.

Weight Control

Weight reduction in overweight patients is extremely important for blood cholesterol control. Weight reduction even in small amounts can enhance the LDL-cholesterol lowering that can be achieved by reducing intakes of saturated fat and cholesterol. For example, 5 to 10 pounds of weight loss can double the LDL-cholesterol reduction achieved by reducing saturated fat and cholesterol. Both weight reduction and exercise not only promote reduction of cholesterol levels but have other benefits (see Figure 2). Thus, they reduce risk for CHD in several ways in addition to lowering LDL-cholesterol levels.

A weight loss program slated for long-term success should include both calorie restriction and regular physical activity. The goal is to achieve a realistic weight loss rather than a marked reduction of weight that cannot be sustained. Very-low-calorie diets (500 to 800 calories/day) are ineffective for achieving long-term weight loss for most patients and are not recommended as the standard approach to weight loss.

Weight reduction may be needed in more patients than are initially identified as being overweight from height-weight tables. This is particularly true for patients with predominant visceral obesity that can be detected by a high waist-to-hip ratio.



Visceral obesity ("pot belly") usually can be recognized by visual inspection without the need for ratio measurements.

A reasonable weight reduction plan for many patients is one that reduces the typical caloric intake by 500 calories per day, although the reduction may vary according to the patient's frame size. Caloric restriction should achieve a gradual weight loss of 1/2 to 1 pound per week. If a patient is severely overweight, a greater caloric restriction may be required, but as stated previously, very-low-calorie diets are not appropriate for most patients. In addition to caloric restriction, regular physical activity is often helpful to achieve and especially to maintain weight loss.

Involvement of the patient in developing appropriate behavior strategies is crucial for successful dietary change and long-term adherence to the recommended diet. Techniques of behavior modification have been helpful for promoting weight reduction, and may be instituted for overweight patients. These techniques focus on unconscious eating habits, compulsive behavior, binge eating, lack of resistance to social pressures for eating

cholesterol-raising foods, use of eating to relieve anxiety and depression, and lack of will power or self-control. The dietary counselor can explore all these areas with the patient and guide him or her in overcoming these eating problems.

Diet Initiation, Monitoring, and Followup

In the outpatient setting, dietary therapy should be initiated when the LDL-cholesterol level has been confirmed to be above 100 mg/dL. At the time of an acute MI, LDL levels frequently are above 100 mg/dL, despite the fall in cholesterol levels caused by the acute event. If the LDL is above 100 mg/dL, the period of hospitalization is a propitious time to begin the Step II diet.

On the Step II diet, a lipoprotein profile should be obtained and adherence to the diet assessed after about 6 weeks. If the goal LDL is not reached in 6 to 12 weeks, there is the option for the motivated patient to further reduce saturated and total fat intakes. If the goal LDL (≤ 100 mg/dL) is attained in 6 to 12 weeks, long-term monitoring can begin. The lipoprotein profile should then be repeated periodically (e.g., every 3 to 6 months), depending on the observed stability of the patient's LDL levels and cardiac status. If the LDL-cholesterol level remains 100 to 129 mg/dL after 6 to 12 weeks, the physician will have to exercise clinical judgment to determine whether drug treatment should be considered.

Dietary therapy, including physical activity and weight control, should be continued even if drugs

are prescribed. The primary aim of dietary therapy is to reduce LDL-cholesterol levels, and it will both enhance the LDL-lowering efficacy and minimize the dose of the prescribed medication. In addition, dietary modification and increased physical activity decrease CHD risk in other ways. Weight reduction and increased physical activity will reduce VLDL and raise HDL levels; weight reduction (combined with decreased salt and alcohol intake) will often lower blood pressure and improve glucose tolerance; and low intakes of saturated fats and cholesterol probably reduce the danger of acute coronary thrombogenesis. Finally, a diet high in fruits, vegetables, grain products, and fish may supply substances (such as antioxidants) that protect against CHD. Thus, the broad range of mechanisms by which dietary modification reduces risk for CHD makes it advisable to continue efforts to follow the recommended diet and life habit changes even if drugs are prescribed.

Drug Treatment

When To Initiate Drug Treatment

Generally, drug treatment is indicated in patients with established CHD if the stable baseline LDL-cholesterol level is 130 mg/dL or greater (Table 3). At these levels, LDL is not likely to fall to 100 mg/dL or less with dietary and life habit changes alone. If the baseline level is in the range of 100 to 129 mg/dL, clinical judgment that weighs potential benefit, possible side effects, and costs must be used in the decision for drug treatment.

LDL-Cholesterol Levels	Diet and Life Habit Changes	Drug Therapy
≤ 100 mg/dL	Yes (LDL monitoring only annually)	No
100–129 mg/dL	Yes	Clinical judgment
≥ 130 mg/dL	Yes	Yes

CHD patients with LDL-cholesterol ≥ 130 mg/dL at the time of hospital discharge should be started on cholesterol-lowering drug therapy because LDL levels are likely to rise as patients become metabolically stable.

Drug Selection

Selection of an appropriate cholesterol-lowering medication for the CHD patient is often important to achieve adequate LDL reduction to reach the goal of 100 mg/dL. The major drugs prescribed for this purpose are statins, bile acid sequestrants, and nicotinic acid. Based on the positive results of clinical trials with statins, including 4S, CARE, and Post CABG, and the large degree of LDL-cholesterol lowering produced by these agents, statins are considered the drug of choice to lower LDL-cholesterol in patients with CHD. Bile acid sequestrants and nicotinic acid are also used, often as part of combination therapy (see Combination Drug Therapy, page 16). Nicotinic acid is useful for raising low HDL levels, a problem frequently encountered in CHD patients. Gemfibrozil can

also be used in combination with statins in selected patients with combined elevations of cholesterol and triglycerides. Reproducible patient handout sheets for statins, bile acid sequestrants, and nicotinic acid are provided on pages 22 to 26.

Statins

As a drug class, statins (the short-hand term for HMG CoA reductase inhibitors) produce the greatest LDL-cholesterol lowering (Table 4). There are currently five statins on the market in the United States: lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin. Statins are used in patients who require significant reduction of their LDL-cholesterol levels. These drugs lower cholesterol by inhibiting HMG-CoA reductase, a key rate-limiting enzyme in the pathway for cholesterol biosynthesis. To meet the intracellular requirements for cholesterol in the face of this inhibition of cholesterol synthesis, LDL receptor function is upregulated, primarily in the liver, thereby lowering serum LDL-cholesterol levels. Treatment with statins in the 4S, CARE, and Post CABG studies produced large reduc-

Available drugs	Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
Major use	To lower LDL-cholesterol
Lipid/lipoprotein effects	LDL-cholesterol: ↓ 20–60 percent HDL-cholesterol: ↑ 5–15 percent Triglycerides: ↓ 10–40 percent
Contraindications	Active or chronic liver disease
Use with caution	Concomitant use of cyclosporine, gemfibrozil, or niacin—increased risk of myopathy
Reduce CHD risk	Yes
Long-term safety	Evidence from about 10 years of extensive clinical use and in 5-year controlled trials
Major side/adverse effects	Elevated hepatic transaminase, myopathy, upper and lower gastrointestinal complaints Statin + anticoagulant may increase prothrombin time

tions in LDL-cholesterol levels and significant benefits in terms of reduced nonfatal MIs and CHD deaths (4S, CARE), reduced total mortality (4S), decreased need for revascularization (4S, CARE, Post CABG), and decreased progression of atherosclerosis in grafted vessels (Post CABG).

The statins are usually given in a single daily dose and should be taken with the evening meal or at bedtime to maximize LDL reduction. The statins are well tolerated by most patients. Occasionally patients have gastrointestinal side effects including dyspepsia, flatus, constipation, and abdominal cramps. These symptoms usually are mild to moderate and generally subside as therapy continues. Infrequent side effects include elevated transaminases and myopathy. Elevated hepatic transaminases occur in approximately 1 percent or less of cases. Myopathy occurs in about 0.1 percent of cases; its frequency is increased when statins are given with cyclosporine, gemfibrozil, or nicotinic acid. Myopathy is rapidly reversible if diagnosed early and treated with discontinuance of drug and hydration, but if the drug is not discontinued, severe myopathy (rhabdomyolysis) can progress to myoglobinuria and acute renal failure. All patients started on statins should be instructed to

report muscle discomfort and weakness or brown urine immediately, and a creatine kinase measurement should be done to check for myopathy.

Bile Acid Sequestrants

Bile acid sequestrants (also called resins) (Table 5) bind with cholesterol-containing bile acids in the intestinal lumen, interrupting the enterohepatic circulation of bile acids and promoting conversion of cholesterol into bile acids in the liver. Reduction of liver cholesterol content stimulates the formation of LDL receptors, which enhances LDL removal from the circulation and lowers serum LDL levels. The major effect of bile acid sequestrants is to lower LDL-cholesterol by about 10 to 20 percent. In some patients, bile acid sequestrants may increase serum triglycerides. Experience with the sequestrants indicates that their long-term use is safe. These drugs are not absorbed from the gastrointestinal tract and lack systemic toxicity. Bile acid sequestrants are useful in patients with moderately elevated LDL-cholesterol levels. Bile acid sequestrants are also highly effective when used in combination with statins for more marked LDL reduction as a result of their additive mechanisms.

Table 5. Summary of Bile Acid Sequestrants

Available drugs	Cholestyramine, colestipol
Major use	To lower LDL-cholesterol
Lipid/lipoprotein effects	LDL-cholesterol: ↓ 10–20 percent HDL-cholesterol: ↑ 3–5 percent Triglycerides: may increase, or no effect
Contraindications	Familial dysbetalipoproteinemia Triglycerides >500 mg/dL
Use with caution	Triglycerides >200 mg/dL
Reduce CHD risk	Yes
Long-term safety	Yes
Major side/adverse effects	Upper and lower gastrointestinal complaints Decrease absorption of other drugs Pancreatitis in patients with hypertriglyceridemia

Cholestyramine and colestipol, the two main bile acid sequestrants, are available as powders or tablets. Bile acid sequestrant powders must be mixed with water or fruit juice and taken once or twice (rarely three times) daily with meals. Tablets must be taken with large amounts of fluids to avoid gastrointestinal symptoms. Sequestrant therapy may produce a variety of symptoms, including constipation, bloating, epigastric fullness, nausea, and flatus.

Although sequestrants are not absorbed, they may interfere with the absorption of other medicines if taken at the same time. Therefore, other medications should be taken at least 1 hour before or 4 to 6 hours after the sequestrant.

Nicotinic Acid

Nicotinic acid (niacin) (Table 6) is a water-soluble B vitamin that can produce favorable effects on all lipids and lipoproteins when given in doses well above the vitamin requirements. Nicotinic acid lowers LDL-cholesterol levels by 10 to 25 percent and triglycerides by 20 to 50 percent, while raising HDL-cholesterol levels by 15 to 35 percent. It can also lower lipoprotein(a) levels, up to 30 percent in some cases. Niacin has been

shown to lower the rate of recurrent MI in CHD patients in the Coronary Drug Project; the treated group also had reduced total mortality in a 15-year followup of that study. All patients taking nicotinic acid to lower serum cholesterol should be closely monitored by trained health professionals to avoid complications from drug toxicity.

Nicotinic acid therapy is especially useful in patients with moderately elevated LDL-cholesterol, elevated triglycerides, and low HDL-cholesterol. Patients on nicotinic acid are usually started on low daily doses (e.g., 125 mg twice daily) and gradually increased to an average daily dose of 1.5 to 3 g per day (crystalline form).

The most common side effect of nicotinic acid is flushing. Most patients develop a tolerance to flushing, and in some patients, it can be decreased by taking the drug during or after meals or by taking aspirin or a nonsteroidal anti-inflammatory drug (NSAID). A variety of gastrointestinal symptoms, including nausea, indigestion, flatus, vomiting, diarrhea, and the activation of peptic ulcers, have been seen with the use of nicotinic acid. Other major adverse effects include hepatotoxicity, hyperuricemia and gout,

Table 6. Summary of Nicotinic Acid

Available drugs	Crystalline nicotinic acid Sustained-release (or slow-release) nicotinic acid (not FDA-approved)
Major use	Useful in most lipid and lipoprotein abnormalities
Lipid/lipoprotein effects	LDL-cholesterol: ↓ 10–25 percent HDL-cholesterol: ↑ 15–35 percent Triglycerides: ↓ 20–50 percent
Contraindications	Chronic liver disease
Use with caution	Non-insulin-dependent diabetes mellitus, gout, or hyperuricemia
Reduce CHD risk	Yes
Long-term safety	Yes for crystalline form; uncertain for sustained-release form
Major side/adverse effects	Flushing, hepatotoxicity (especially for sustained-release form), hyperglycemia, hyperuricemia or gout, and upper gastrointestinal complaints

and hyperglycemia. Risk of these effects increases as the dose of nicotinic acid is increased. Rare side effects are toxic amblyopia, acanthosis nigricans, and myopathy.

Fibrates

The cholesterol-lowering drugs called fibrates (fibric acid derivatives) are used primarily in patients with high triglyceride levels. Gemfibrozil is the fibrate most commonly used in the United States. Fibrates are primarily effective in lowering triglycerides and, to a lesser extent, in increasing HDL-cholesterol levels. Gemfibrozil is not recommended by the Food and Drug Administration as single drug therapy for patients with CHD.

Fibrates are usually given in two daily doses 30 minutes before the morning and evening meals. The reductions in triglycerides generally are in the range of 20 to 50 percent, with increases in HDL-cholesterol of 10 to 15 percent. Gemfibrozil generally reduces LDL-cholesterol by 10 to 15 percent in patients whose only abnormality is elevated LDL; however, LDL-cholesterol may be increased in patients with elevated triglycerides.

Fibrates are generally well tolerated by most patients. Gastrointestinal complaints are the most common side effects. Fibrates increase the lithogenicity of bile, which increases the likelihood of developing gallstones. Fibrates can potentiate the effect of anticoagulants. The addition of gemfibrozil to statin therapy increases the risk of myopathy; this combination should therefore be used only in selected patients with combined hyperlipidemia. Patients must be alerted to the increased risk of severe myopathy.

Hormone Replacement Therapy

The risk of CHD is increased in postmenopausal women, whether the menopause is natural, surgical, or premature. This increasing risk may be related to the loss of estrogens after menopause. Hormone replacement therapy (HRT) may be prescribed when women begin to experience symptoms from menopause.

There is currently no clinical trial evidence proving conclusively that CHD event rates are reduced through the use of HRT. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial looked at the effect HRT has on CHD risk factors. Results from the PEPI study showed that:

- Estrogen-only therapy raised the level of HDL-cholesterol.
- Combined estrogen-progestin therapies also increased HDL levels, although less than estrogen alone.
- All the hormone regimens decreased the level of LDL-cholesterol about the same.
- Fibrinogen levels were decreased by all the hormones, which may be a desirable change.
- None of the hormone regimens caused a significant weight gain.
- All the hormone regimens caused some rise in triglyceride levels.

The beneficial effect of HRT on lipid levels (15 percent LDL reduction) would favor its use in many women with CHD. If LDL is elevated slightly above the 100 mg/dL goal, HRT can be considered an appropriate lipid-lowering therapy in postmenopausal women with CHD. If HRT does not enable the patient to reach her goal, or if LDL-cholesterol levels are moderately elevated at baseline, HRT may be combined with other cholesterol-lowering drugs to reach the LDL goal of 100 mg/dL or less.

Combination Drug Therapy

In most patients with CHD, therapy with a single drug in conjunction with diet therapy should be adequate. In many patients with only modest elevations of LDL-cholesterol, low doses of drug combined with diet therapy will suffice; however, greater elevations of LDL require more intensive drug treatment. It is important to use doses of statins adequate to reach the LDL target of 100 mg/dL. If the goal of therapy is not attained after 3 months with single drug therapy, however, consideration can be given to adding a second

Table 7. Drug Selection for Combination Therapy

Lipid Levels	Single Drug	Combination Drug
Elevated LDL-cholesterol and triglycerides <200 mg/dL	Statin	Statin + BAS
	Nicotinic acid (NA)	Statin + NA*
	Bile acid sequestrant (BAS)	NA + BAS
Elevated LDL-cholesterol and triglycerides 200–400 mg/dL	Statin	Statin + NA*
	Nicotinic acid	Statin + Gemfibrozil†
		NA + BAS
		NA + Gemfibrozil

* Possible increased risk of myopathy and hepatitis.

† Increased risk of myopathy. Must be used with caution.

agent (see Table 7). The decision to proceed with more aggressive combination drug therapy in CHD patients must be made after counseling the patient about potential side effects. These drawbacks, however, may be more than offset by regression or slowed progression of atherosclerosis and reduction in cardiovascular events and mortality. In addition, it may be possible to avoid some of the drawbacks of combination therapy by using low doses of each drug.

Some patients with marked elevations of LDL-cholesterol, especially those with severe forms of hypercholesterolemia, may not achieve LDL-cholesterol levels of 100 mg/dL or less, even when diet therapy is combined with combination drug therapy. Even so, clinical trials indicate that a major reduction in CHD risk occurs when there is a substantial LDL-cholesterol reduction (30 to 40 percent), even if the target goal of 100 mg/dL or less is not reached. Thus, aggressive LDL-cholesterol lowering should be pursued in all CHD patients with elevated levels of LDL-cholesterol.

Combination of a bile acid sequestrant with either nicotinic acid or a statin has the potential of lowering LDL-cholesterol levels by 40 to 50 percent or more. For most patients, the judicious use of one or two drugs should provide an adequate LDL-cholesterol-lowering effect. Most

cholesterol-lowering drugs can be used in combination. Nonetheless, a statin plus fibrate carries an increased risk of myopathy, whereas a statin plus nicotinic acid may increase the likelihood of hepatotoxicity, and possibly myopathy.

Monitoring and Followup

With good drug adherence, maximum lowering of LDL-cholesterol is achieved at any given dose of lipid-lowering medication within 4 to 6 weeks of initiating or changing therapy. Followup LDL determination and assessment of possible adverse biochemical changes should be made 6 to 8 weeks after initiating or changing drug therapy. Nicotinic acid is an exception to this guideline; repeat measurements should be made when the nicotinic acid dose has been stable for 4 to 6 weeks (e.g., 1,500 mg per day plateau).

After the target LDL-cholesterol concentration has been achieved, patients should be followed at 2- to 3-month intervals through the first year. If the target LDL-cholesterol is not achieved with the initial dose, then drug titration should be used to find the optimum dose. Drugs that must be titrated to maximum efficacy are the statins, nicotinic acid, and the bile acid sequestrants. Gemfibrozil is prescribed in a single dosage schedule.

After 1 year of therapy during which the response has been established and there is no evidence of biochemical toxicity, patients may have their lipid levels monitored at 4- to 6-month intervals; more frequent followup may be dictated by their cardiac status. Measurements to check for toxicity should be obtained at the same time as assessment of lipid and lipoprotein levels. When placing patients on cholesterol-lowering therapy, as with any drug, it is important that patients be asked to report any side effects they experience.

Patients should be advised that an elevated cholesterol, like many other disorders, is not cured but is only controlled by diet and drug therapy. Discontinuation of treatment is quickly followed by a rise of the cholesterol and a return of the CHD risk to the high level that existed before therapy was started.

ADHERENCE

Cholesterol reduction in CHD patients is highly effective in reducing CHD events—but it has to be maintained. The challenge is to combine the efforts of professionals with those of patients and their families to maximize the likelihood that cholesterol-lowering treatment will be properly initiated and adhered to. Primary care physicians, cardiovascular specialists, nurses, registered dietitians, and pharmacists need to work as a team to maximize the quality of patient care and the likelihood that patients will follow the treatment regimen.

Role of the Physician

Cholesterol lowering should be an integral part of the routine management of CHD—no less so than aspirin and beta-blockers, whose capacity to reduce the risk of recurrent CHD events is equaled by cholesterol lowering. Primary care physicians will often be the ones to identify the need to lower the CHD patient's cholesterol level in an outpatient setting. They will therefore be responsible for initiating cholesterol-lowering

therapy and, if necessary, providing a referral to a cardiovascular specialist, and possibly a dietitian, for help in managing coronary disease.

Cardiovascular specialists will probably be the ones who are responsible for the identification and treatment of an elevated blood cholesterol in CHD patients suffering an acute event. The hospital stay provides a good opportunity to start treatment. At discharge, if LDL-cholesterol is 130 mg/dL or higher, diet/lifestyle therapy together with drug treatment should be initiated. For patients with LDL-cholesterol between 100 and 129 mg/dL, diet should be initiated and the LDL-cholesterol remeasured in 6 weeks. Cholesterol-lowering therapy after discharge should be a coordinated effort between the cardiovascular specialist, the primary care physician, and the patient.

A key aspect in the coordination of cholesterol-lowering therapy is the communication between the physician and the patient. Key topics that need to be addressed at the outset include:

- **Rationale for treatment**
 - Appraisal and significance of the lipid abnormality
 - Potential benefits of treatment
 - Goals of treatment
 - Treatment plan
- **Step II diet**
 - Plan for adoption and maintenance of the diet
 - Key dietary changes to be made
 - Nutrition professionals available for assistance
- **Other life habit changes**
 - Prescription for physical activity and, if necessary, weight loss
- **Drug treatment**
 - Whether drug therapy is in the picture now, or possibly later

These topics and others are covered in an easy-to-digest manner in the National Cholesterol Education Program patient booklet, *Live Healthier, Live Longer: Lowering Cholesterol for the Person With Heart Disease*. Giving your patient a copy of the booklet will help him or her get started on cholesterol-lowering treatment and will support long-term adherence as well (see order form on page 31).

During long-term followup visits, routine inquiries about the patient's adherence to the treatment program help reinforce the importance given it by the physician. In addition, responding to the patient's questions and concerns can help overcome barriers to long-term adherence to the treatment regimen.

Role of the Nurse

The patient's long-term success in controlling cholesterol can be greatly enhanced by involvement of the office, clinic, or home health care nurse. Nurses are health professionals trained to provide health education and interpret health behavior. Particularly important is the nurse's role in reinforcing and interpreting the instructions provided by the physician. In addition, the nurse can provide detailed instruction on practical approaches to adherence. Nurses are also able to provide support to patients who are following long-term treatment programs by discussing problems and challenges that are encountered.

Role of the Registered Dietitian

The registered dietitian or other qualified nutrition professional is particularly important to patients with CHD for ensuring nutritional adequacy and balance on the Step II diet. Dietitians with particular expertise in cholesterol management are available in most large medical centers where they are often part of a multidisciplinary lipid clinic or cardiac rehabilitation team. They can also be identified through the American Dietetic Association referral hotline (800-877-1600). Dietitians are best equipped to interpret

the patient's nutritional habits and to offer detailed, practical instructions on carrying out dietary treatment programs, such as how to shop for groceries, prepare tasty low-saturated-fat foods at home, select foods from restaurant menus, and follow the prescribed diet when traveling.

Role of the Pharmacist

The community or clinic pharmacist can also play an important role in promoting long-term cholesterol control, particularly for patients with cholesterol levels that require cholesterol-lowering drug therapy. These professionals often have the greatest contact with the patient who is undergoing long-term treatment and are readily accessible in most communities. Their interaction with the patient should begin with the patient's first prescription for cholesterol-lowering therapy and continue as the patient returns periodically for prescription refills. The pharmacist has the opportunity to reinforce and extend instructions to the patient about how, why, and when to take the prescribed medication. The pharmacist can also provide support to patients on long-term therapy by advising how to overcome side effects and other problems that may interfere with adherence to the treatment program.

By working as a team, health professionals can provide a consistent message that reinforces positive health behaviors. This message will support long-term adherence to both lifestyle changes and drug therapy, thereby promoting the most effective treatment of the patient's CHD risk.

Strategies To Enhance Adherence

To be maximally effective in achieving long-term cholesterol control, each health professional involved in the patient's care should be aware of and effectively utilize techniques that have been shown to be effective in enhancing adherence to treatment regimens. Following is a summary of some of these strategies.

- Teach the patient the treatment regimen.
 - Diet/lifestyle therapy
 - Provide patients with practical ways to cut back on saturated fat, total fat, and cholesterol.
 - Provide patients with a referral to a dietitian or other qualified nutritionist.
 - Instruct patients on the benefits of physical activity and provide them with a personalized exercise prescription.
 - Provide realistic goals for weight control and maintenance.
 - Drug treatment
 - Teach patients how to take their medication.
 - Teach patients to recognize and manage side effects.
 - Teach patients to manage missed doses.
 - Make sure patients know how to contact someone if they need assistance.
- Give patients a copy of *Live Healthier, Live Longer: Lowering Cholesterol for the Person With Heart Disease* (see order form on page 31). It provides valuable assistance in teaching patients the treatment regimen and encouraging long-term adherence.
- Help the patient identify ways to remember medication doses. For example:
 - Tie doses to daily rituals, such as coinciding doses with meals.
 - Set alarm clocks or watches to signal dosing times.
 - Place reminder cards in prominent places in the home.
 - Have spouses or friends remind them of doses.
 - Send reminders of appointments and medication refills.
 - Use a daily medication box or blister packaging to organize and prompt drug doses.
- Develop reinforcers of adherence.
 - Encourage patients to follow the progress of their therapy by keeping logs of cholesterol levels and other clinical markers (see example below).
 - Review patient logs periodically to reinforce adherence.
 - Reward positive treatment outcomes—e.g., praise the patient for good control.
- Anticipate common problems and teach patients how to manage them. Poor adherence may occur because the patient lacks knowledge about what to expect from medications and what to do if unexpected events occur.
 - Teach patients about common side effects of their medication and how to minimize and manage them.
 - Teach patients to identify and interpret symptoms.
 - Teach patients how to initiate self-treatment if appropriate.
 - Teach patients when to call for help.

Cholesterol-Monitoring Log						
Date	Medication Name	Dose	LDL-Cholesterol	Total Cholesterol	HDL-Cholesterol	Triglycerides

- Involve a spouse, family member, or friend in the patient's therapy program. One of the strongest influences on adherence is a family member or close friend. Involve someone who is close to the patient when providing the initial instructions (with the patient's permission) and encourage the individual to support the patient's long-term treatment program.
- Establish a supportive relationship with the patient. Patients are more likely to adhere to treatment regimens if they like their health professionals, trust their advice, and perceive a caring attitude. Listening carefully to the patient's questions, concerns, fears, and misconceptions about illnesses and treatments can facilitate effective counseling.
- Make adherence important by asking about it. Periodically asking about adherence helps underscore the importance placed on it by the health professional, but care should be taken to encourage rather than blame the patient.
- Provide ongoing education and updates about the patient's illness and treatment. Provide updates about the patient's therapy as new information becomes available and as their level of understanding increases.

SUMMING UP

Cholesterol lowering in CHD patients is highly effective in reducing the risk for MI and death from CHD. There is almost no treatment that offers CHD patients more benefit in reducing CHD risk. Cholesterol lowering should therefore be as routine a part of CHD management as aspirin. Careful attention to initiating appropriate cholesterol-lowering therapy and sustaining it will improve the health and prolong the lives of millions of Americans who have CHD.

PATIENT HANDOUT

Patient Instructions for Taking Statins

Statins are also known as “HMG CoA reductase inhibitors,” because they block the action of an enzyme or chemical substance called “HMG CoA reductase” that is important in cholesterol production in the body. The statins currently include lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin. These prescription medications are extremely effective in lowering blood cholesterol levels and lowering the risk of heart attack. They have been used safely for about 10 years by patients with elevated blood cholesterol. The primary benefit of statins is their ability to lower LDL-cholesterol (which some people call the “bad” cholesterol). Your starting dose of _____ will be _____ milligrams daily. This dose will be adjusted based on your cholesterol levels at future visits. To obtain the best results with your statin medication, follow the instructions below.

Taking Statins

Statins work best if they are taken in the evening because this is when the body makes the most cholesterol. You should also try and take your statin medication when you have food in your stomach. It may be most convenient to take your statin with or just after your dinner (supper) or your bedtime snack.

Questions

If you have any questions or problems while taking your statin, please call us during the day at _____ or at night at _____.

Take Your Statin Regularly

To get the full reduction in cholesterol levels, it is important to take your entire dose each day. Do not take more than this in any one day. If you should forget to take a dose until the next day, skip it. Do not try and catch up with missed doses; instead, continue with the next scheduled dose.

Side Effects

Most people do not experience serious side effects from statins. Occasionally patients have mild to moderate side effects such as upset stomach, gas, or constipation. These symptoms usually go away as the body gets used to the new medication.

Infrequently, there may be a problem with liver enzyme changes. Even less often there may be muscle problems. If you have muscle pain or weakness or brown urine, you should call the number below immediately. You will need a blood test to find out if you are really having a muscle problem, and if so, you will need to stop the medication.

Side effects are more likely to appear when you first start taking statins and just after increasing the daily dose. If you should notice any side effects with your new medicine, please call our office at the number below.

While taking this medication, you will need routine blood tests to monitor the effect of the medication on liver function and cholesterol levels. It is extremely important to obtain these blood tests as scheduled.

PATIENT HANDOUT

Patient Instructions for Taking Resin Therapy

You have been given one of the following medications to lower your blood cholesterol level: colestipol or cholestyramine. These medications are generally referred to as bile acid sequestrants, bile acid resins, or simply resins. Resins lower blood cholesterol levels by binding bile acids in the intestines and causing more of the cholesterol in the bloodstream to be converted into bile acids and eliminated from the body through the stool. To get the best results with resin therapy, follow the instructions below.

Preparing Your Resin

Your doctor will prescribe either resin powder or tablets. Resin tablets do not need to be prepared, but must be taken with large amounts of fluid.

If your doctor prescribes resin powder, you must mix it in a beverage or other fluid before you take it (see below for instructions). NEVER take this medicine in its dry form, as it may cause you to choke.

- a. Mix the contents of a packet or scoop of powder with your choice of beverage. We recommend noncarbonated beverages such as juices, milk, or just water. Carbonated beverages may cause air to be entrapped, which could cause belching. You may experiment with different beverages until you find the one you like.

To mix your powder with a beverage, pour it into a cup or glass. Add two or more ounces of the beverage you have chosen, stir it vigorously (some people use a mixer for this), and drink. Note that the powder will not totally dissolve in the liquid but should be suspended by the stirring and thus be easier to drink. You may follow this with a swallow or two of

the beverage to wash down any powder remaining in your mouth. To reduce side effects, drink at least 2 to 6 ounces of fluid per packet/scoop of resin powder you take.

You can drink your medication immediately, or you can mix larger doses and store refrigerated for up to 2 days. Many patients find that mixing their medications with fluids in advance allows time for the beads of medication to swell and have a less "gritty" taste and feel.

- b. You may also mix the contents of the packet or scoop of powder in a highly fluid food or fruit. Examples include applesauce, soup, and pulpy fruits such as crushed pineapple, pears, peaches, or fruit cocktail.

To mix the powder with food, pour the contents of a packet or scoop into a bowl, add at least 6 ounces of the food chosen, mix it well, and eat.

Dose of Resin

The dose of resin that will produce the greatest lowering of blood cholesterol levels is between four and six scoops or packets of powder daily mixed with a beverage. You will need to help us determine the dose that works best for you without causing unpleasant side effects. To do this, start by taking only one packet or scoop of powder daily with dinner (supper). If you are able to take this dose without problems for a week or two, increase your dose to two packets or scoops of powder, one with breakfast and one with dinner. After you have successfully taken this dose for 1 or 2 weeks, increase your dose to three packets or scoops of powder each day. Continue with this plan until you have arrived at the best dose for you. Although six doses per day is ideal, we will be content with whatever dose you can comfortably take each day, especially if it produces a good cholesterol-lowering effect. Most patients take between two and four doses per day.

Times To Take Your Dose of Resin

Take the dose of powder mixed with a beverage just before or with meals. If you choose to take only one dose each day, take it with the heaviest meal (usually dinner or supper for most people). If you choose to take it twice daily, take it with the two heaviest meals or with the most convenient meals. This is usually breakfast and dinner (supper). When you increase your dose to three packets or scoops of powder per day, you may take one dose three times a day with each meal, instead of once or twice daily, if you prefer.

If you are taking other medications, please check on the exact time to take the resins because they may interfere with absorption of other medications from the intestines. As a general rule, you should take your other medications 1 hour before or 6 hours after you take your resin.

Take Resin Regularly

To achieve the best effects from the medication, it is very important to consistently take the same number of doses of medication each day. If you forget the morning dose, take it with lunch. If you forget the dinner dose, take it later in the

evening with a light snack. If you should forget your dose until the next day, do not try to catch up with the missed doses; instead, continue with the next scheduled dose.

Side Effects

Resins are not absorbed into the bloodstream, but pass directly through the gastrointestinal tract, binding with bile acids and cholesterol along the way and eliminating them with the stools. If side effects occur, they will be limited to the stomach and intestines and will occur during the early days of therapy. Some symptoms associated with these medications include constipation, bloating, gas, and heartburn.

Constipation may be relieved by increasing fluid and dietary fiber or by commercial products containing fiber, such as psyllium. Bloating or gas may be relieved by trying to avoid swallowing air when taking the resin mixture. Once the body has gotten used to the medication, side effect symptoms (if they occur at all) will lessen. Please call us if you experience any discomfort while taking this medication so that we can advise you of ways to lessen them.

Questions

If you have any questions or problems while taking your resin, please call us during the day at _____ or at night at _____.

PATIENT HANDOUT

Patient Instructions for Taking Nicotinic Acid (Niacin)

Niacin or nicotinic acid is a B vitamin that effectively lowers blood cholesterol levels. It has been used safely for several decades by patients with high blood cholesterol. It has the advantage of not only lowering total cholesterol and LDL-cholesterol (which some people call the "bad" cholesterol) but also lowering triglycerides and raising HDL-cholesterol (which some people call the "good" cholesterol). It has been used in major studies of cholesterol-lowering therapy, which show that it is associated with a decreased risk of heart attacks and a reduction in the buildup of atherosclerosis (plaque) in coronary blood vessels.

Follow the instructions below to obtain the best effects with niacin.

Dosage Forms of Niacin

Niacin or nicotinic acid is available in two forms. Both forms lower the blood cholesterol, but there are important differences you should know about.

- Immediate release. A tablet or capsule that will dissolve in your stomach within minutes after you swallow it and release niacin quickly into your bloodstream.
- Extended release. This form may produce less flushing, but it is not recommended for routine use because of increased risk of liver problems. This form is not approved by FDA for treatment of cholesterol disorders.

Nicotinamide is sometimes referred to as niacin, but it does not lower cholesterol. Please try to purchase the same brand of niacin each time. If you should change brands, please notify your doctor's office. To ensure that you have chosen the appropriate form of niacin, check with your pharmacist.

Dose of Niacin

The dose of niacin must be carefully adjusted in each patient to effectively lower blood cholesterol levels and to minimize side effects. Generally, total daily doses between 1,500 milligrams (mg) and 3,000 mg are required. However, you should slowly work up to this dose level. One schedule for doing this is presented below. If you are having side effects, go slower.

First week:	125 mg twice daily
Second week:	250 mg twice daily
Third week:	500 mg twice daily
Fourth week:	750 mg twice daily
Fifth week:	1,000 mg twice daily
Sixth week:	1,500 mg twice daily

We will inform you when you should make another clinic visit. We would like to see you 4 to 6 weeks after you have attained a total daily dose of _____ mg of niacin.

Taking Niacin

Before taking a dose of niacin, FIRST take one adult aspirin tablet (325 mg) or a dose of the nonprescription medication ibuprofen 30 minutes before your morning dose of niacin. Enteric-coated aspirin is preferred because it is less bothersome to the stomach. Repeat this every morning for the first 14 days when you first begin niacin therapy or each time you increase your daily dose.

- a. Taking aspirin or ibuprofen will reduce any flushing, warm feeling, tingling, or headache symptoms that niacin may cause. These symptoms may occur when first beginning niacin therapy. They are not harmful and are to be expected with this medication. The symptoms occur because niacin increases the flow of blood throughout the body by dilating (widening) blood vessels. The aspirin or ibuprofen will reduce this effect without

lessening niacin's effect on cholesterol. In time, the body should develop a tolerance to these symptoms to the point that they are no longer bothersome.

- b. Note that each time niacin therapy is stopped, these symptoms may reappear when it is restarted. Also, these symptoms may appear each time the dose of niacin is increased. Thus, be sure to take one aspirin or ibuprofen dose every day for several days each time niacin is restarted or the dose is increased.
- c. Try to take niacin when you have food in your stomach. It may be most convenient to take a dose with or just after breakfast (or lunch) and with or just after dinner (supper). This will reduce any nausea, gas, or heartburn symptoms that niacin may cause. If these symptoms occur at all, they are more likely to occur soon after starting niacin. They probably occur because niacin is a weak acid and may irritate the stomach. Taking niacin with food should help buffer the acid and reduce these symptoms.

Take Niacin Regularly

To have the best reduction in cholesterol levels and particularly to avoid side effects, it is VERY important to take your entire dose of niacin each day. Do not take more than this in any one day. If you should forget your morning dose, take it later in the evening with a light snack. If you do not remember that you missed a dose until the next day, skip it. Do not try to catch up with missed doses, as they may increase side effect symptoms. Some patients may find it easier to take three doses of niacin a day.

Questions

If you have any questions or problems while taking your niacin, please call us during the day at _____ or at night at _____.

Side Effects

As pointed out, tingling, warm feelings, headaches, nausea, gas, and heartburn may occur with niacin. In addition, niacin may cause diarrhea, fatigue, itching, or a rash. Like the other symptoms, these are not harmful, but may be bothersome. Also, like the other symptoms, they will lessen once the body has gotten used to the medication. Itching and the rash may be caused by an increased flow of blood throughout the body and may also be reduced with the dose of aspirin or ibuprofen taken along with niacin.

In general, side effect symptoms are more likely to appear just after you first start taking niacin and just after increasing the daily dose. Taking aspirin or ibuprofen daily and taking niacin doses with food should reduce these symptoms. As you continue to take niacin, you should notice that these symptoms will diminish or disappear.

If side effect symptoms are intolerable, reduce your total daily dose by one tablet or capsule. For example, if you are taking two capsules twice a day with breakfast and dinner, reduce your dose to one capsule with breakfast and two capsules with dinner (or one capsule three times a day with each meal). Once your body adjusts and the symptoms have disappeared, increase your dose back to two capsules twice daily. If these symptoms continue to be a problem, please call your doctor.

While taking this medication, you will also need routine blood tests to be sure that other side effects are not occurring. These blood tests may include tests of liver function, glucose, and uric acid. It is extremely important to obtain these as scheduled.

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ADDITIONAL MATERIALS

The NHLBI Information Center is a service of the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. The Information Center provides information to health professionals, patients, and the public about the treatment, diagnosis, and prevention of heart, lung, and blood diseases.

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Below is a list of additional materials obtainable from the NHLBI Information Center. Please use the order form that follows.

Professional Publications

- ❑ *Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II)* (NIH Publication No. 93-3095, \$5.00 each; package of 25, \$106.25; package of 100, \$400.00)

Clinical practice guidelines for detecting, evaluating, and treating high blood cholesterol in adult patients. Full report with references.

Patient and Public Materials

- ❑ *Live Healthier, Live Longer: Lowering Cholesterol for the Person With Heart Disease* (NIH Publication No. 96-3805, \$3.00 each; package of 25, \$37.50; package of 100, \$120.00)

An essential handbook for CHD patients designed to help lower blood cholesterol levels to reduce the risk of a future heart attack and prolong life.

- ❑ *Step by Step: Eating To Lower Your High Blood Cholesterol* (NIH Publication No. 94-2920, \$3.50 each; package of 25, \$60.00; package of 100, \$225.00)

An information-packed booklet giving down-to-earth advice on how to make diet and lifestyle changes to lower high blood cholesterol.

- ❑ *So You Have High Blood Cholesterol* (NIH Publication No. 93-2922, \$3.00 each; package of 25, \$37.50; package of 100, \$120.00)

A booklet explaining what patients need to know about cholesterol, including how to lower it and where to go for help. Intended primarily for patients without CHD, but includes some information for CHD patients as well.

- ❑ *Facts About Blood Cholesterol* (NIH Publication No. 96-2696, single copy, free; each additional copy, \$1.00; package of 25, \$12.50; package of 100, \$40.00)

A fact sheet for the public providing basic information on cholesterol, how it's tested, and what can be done to control it.

- ❑ *Eat Right To Lower Your High Blood Cholesterol* (NIH Publication No. 92-2972, \$1.50 each; package of 25, \$18.75; package of 100, \$60.00)

An easy-to-read pamphlet providing basic information about how simple dietary changes can lower blood cholesterol. Geared to Step I diet for primary prevention, not Step II for CHD patients.

- ❑ *Check Your Cholesterol and Heart Disease I.Q.* (NIH Publication No. 95-3794, single copy, free; each additional copy, \$.50; package of 25, \$6.25; package of 100, \$20.00)

A 12-question true-false quiz testing the reader's general information on how cholesterol affects the heart.

- ❑ *Check Your Physical Activity and Heart Disease I.Q.* (NIH Publication No. 96-3795, single copy, free; each additional copy, \$.50; package of 25, \$6.25; package of 100, \$20.00)

A 12-question true-false quiz addressing physical activity and heart health.

- ❑ *Facts About Heart Disease and Women: Self-Help Strategies for a Healthy Heart—Reducing High Blood Cholesterol* (NIH Publication No. 96-3658, single copy, free; each additional copy, \$1.00; package of 25, \$12.50; package of 100, \$40.00)

A fact sheet of self-help information to help women lower blood cholesterol levels.

- ❑ *Exercise and Your Heart: A Guide to Physical Activity* (NIH Publication No. 93-1677, \$3.00 each; package of 25, \$37.50; package of 100, \$120.00)

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